Research results

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My research focus on the interaction of ABIN and linear poly-ubiquitin chain. A20-binding inhibitor of NF-κB activation (ABIN) involves in inhibition of an important transcription factor, NF-κB which manipulates several cellular functions including inflammatory, apoptosis and development. Aberrant NF-κB regulation may lead to several diseases such as cancer, autoimmune disease and improper immune development. Therefore, understanding the molecular mechanism in regulation of NF-κB is critical and necessary for human health. NF-κB is a transcription factor which is held in cytoplasm by an inhibitor protein IκBs (Inhibitor of NF-κB), upon stimulation by inducers, IκBs will be phosphorylated by IKK complex and lead to its proteasomal degradation. Freed NF-κB can translocate into nucleus to regulate the downstream genes. Ubiquitin, a small protein with 76 amino acids which is correlated with post-translational modification (PTM) and plays a vital role in regulation of NF-κB signaling pathway. Through the sequential enzyme events, ubiquitin can be tagged onto its target protein by formation of isopeptide bond between carboxyl group of ubiquitin and ε-amino group of substrate. Through its internal 7 lysine residues, ubiquitin can be ligated into longer poly-ubiquitin chain while this process is called ubiquitination. Recently, an emerging new discovery of ubiquitin chain has been found which is Met-1-linked polyubiquitin chain, also known as linear poly-ubiquitin chain. These head-to-tail type of poly-ubiquitin chain only present in NF-κB signaling pathway and maintain the NF-κB homeostasis in cells. Therefore, the proteins interacting with linear poly-ubiquitin chain is important in NF-κB signaling pathway. ABINs belong to UBAN (UBD in ABIN proteins and NEMO) family and interact with linear poly-ubiquitin chain by its UBAN domain to turn down the NF-κB signaling pathway. Previous studies have shown that the ABIN-UBAN domain mutations will disrupt the interaction between ABIN and linear poly-ubiquitin chain and leads to autoimmune diseases so it is vital to understand their interaction mechanism. In our study, we solved the protein complex structure of ABIN and tetra-ubiquitin and found a unique binding mode between ABIN and tetra-ubiquitin. We also identified these disease-cause mutations will disrupt their binding. Besides, we are curious about the role of longer poly-ubiquitin chains in cell, so we perform several biochemical assays and found that longer poly-ubiquitin chains attend to recruit ABINs, causing aggregation of ABINs. This may suggest that ABINs inhibit NF-κB activation by competing the ubiquitin binding site with NEMO or perform as an adaptor to gather A20, an inhibitory of NF-κB working together to turn down the

NF-κB pathway. In conclusion, my work show the detail protein-protein interaction of ABIN with linear poly-ubiquitin and demonstrate the possible regulation mechanism of inhibition NF-κB pathway in cell.

Reference

SM Lin, SC Lin, JY Hong, TW Su, BJ Kuo, WH Chang, YF Tu, Yu-Chih Lo*. Structural Insights into Linear Tri-Ubiquitin Recognition by A20-Binding Inhibitor of NF-κB (ABIN)-2. **Structure**. 25, p66-78. (2017) *corresponding author